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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,466	09/10/2004	Mark Ostermeier	56908(71699)	1259

21874 7590 12/29/2006

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/29/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,466	OSTERMEIER, MARK	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,14,26,30,32,38,39 and 41* is/are pending in the application.

4a) Of the above claim(s) *26,30,32,38,39 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-29-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group I, claims 1-25, in the reply filed on 11-29-06 is acknowledged. The traversal is on the ground(s) that multiple groups can be examined together without undue burden. Groups I and II both include the subject matter of a modulatable fusion molecule comprising an insertion sequence and an acceptor sequence, wherein the insertion couples the state of the insertion sequence to the state of the acceptor sequence. This is not found persuasive because The common "special technical feature" shared by groups I-V is a method of assembling a fusion molecule by inserting an insertion sequence into an acceptor sequence and the insertion sequence and the acceptor sequence each comprises a state, thereby generating a fusion molecule. Siegel et al., 2000 (Methods in Enzymology, Vol. 327, p. 249-259) teaches generation of a fusion protein by fusing GFP in-frame into the middle of a signal transduction protein (detector) so that conformational rearrangement in the detector perturb the fluorescence of GFP via the use of expression vector having DNA sequence encoding the GFP and signal transduction protein under the control of cell-specific promoter (Figure 1). Siegel also engineered a chimeric protein having modified GFP fused in-frame at a site just after the 6^{th} transmembrane segment of a voltage-activated Shaker K+ channel, and a point mutation is introduced into the pore of the channel so as to prevent ion conduction but preserve the gating rearrangements of the channel in response to voltage changes (p. 252). Generation of the GFP fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state or the acceptor sequence. Therefore, no "special technical feature" has been contributed by the present application over the prior art. Thus, groups I-V do not relate to

a single general inventive concept under PCT Rule 13.1. There is serious burden for examiner to search all the groups.

The requirement is still deemed proper and is therefore made FINAL.

Claims 26-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11-29-06.

It has come to examiner's attention that a preliminary amendment was filed on 9-10-04 and said preliminary amendment has been entered. Claims 9-13, 15-25, 27-29, 31, 33-37, 40 and 42-44 have been canceled. Claim 26 has been amended. Since applicant has elect group I, claims 1-25, for examination, therefore, claims 1-8 and 14, according to the preliminary amendment filed 9-10-04, will be examined by examiner. Thus, claims 1-8, 14, 26, 30, 32, 38, 39 and 41 are pending. Claims 26, 30, 32, 38, 39 and 41 are withdrawn from consideration. Claims 1-8 and 14 are under consideration.

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The filing date of the PCT US03/07380 should be 3-10-**03** rather than 3-10-02.

Specification

2. The disclosure is objected to because of the following informalities: The term "CLAIMS" in line 1 of page 70 should be changed to "I claim:" or "What is claimed is:".

Appropriate correction is required.

3. The disclosure is objected to because of the following informalities: The amendment filed 3-24-05 indicates that there are SEQ ID Nos. 29-38 in Figure 2A, however, there are 12 single strand nucleotide sequences or 6 double strand sequences. The number of sequence of SEQ ID Nos. 29-38 do not match the number of sequences in Figure 2A. Furthermore, there are only 2 nucleotide sequences in Figure 3A rather than 3 sequence of SEQ ID Nos. 39-41.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-8 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Siegel et al., 2000 (Methods in Enzymology, Vol. 327, p. 249-259, IDS).

Claims 1-6 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence. Claims 2-3

specify the state of the insertion sequence is modulated and in response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the insertion sequence, respectively. Claim 6 specifies the fusion molecule comprises a new state. Claims 7-8 are directed to a method for assembling a fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence. Claim 14 is directed to a method for assembling a multistable fusion molecule which can switch between at least an active state and a less active state comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, wherein the respective other sequence is responsive to a signal, and selecting a fusion molecule, wherein the state is coupled to the signal such that the fusion molecule switches state in response to the signal.

Siegel teaches generation of a fusion protein by fusing GFP in-frame into the middle of a signal transduction protein (detector) so that conformational rearrangement in the detector perturb the fluorescence of GFP via the use of expression vector having DNA sequence encoding the GFP and signal transduction protein under the control of cell-specific promoter (Figure 1). Siegel also engineered a chimeric protein having modified GFP fused in-frame at a site just after the 6^{th} transmembrane segment of a voltage-activated Shaker K+ channel, and a point mutation is introduced into the pore of the channel so as to prevent ion conduction but preserve the gating rearrangements of the channel in response to voltage changes (p. 252). Generation of the GFP fusion protein

constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. GFP can be considered as an insertion sequence and the Shaker K+ channel can be considered as an acceptor sequence, which has a point mutation. Conformational rearrangement in the detector can be considered a signal, which perturbs the fluorescence of GFP. Therefore, the fusion molecule switches state in response to the signal. Thus, claims 1-8 and 14 are anticipated by Siegel.

6. Claims 1-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Kratz et al., 1999 (PNAS, Vol. 96, pp. 1915-1920).

Claims 1-6 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence. Claims 2-3 specify the state of the insertion sequence is modulated and in response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the insertion sequence, respectively. Claim 6 specifies the fusion molecule comprises a new state. Claims 7-8 are directed to a method for assembling a fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence.

Kratz teaches preparation of DNA construct for producing GFP fusion protein, wherein the entire GFP sequence, flanked on both sides by Gly-rich linkers, is inserted into the central c/el epitope of the truncated, assembly-competent core protein derivative core 1-149 of hepatitis B virus (HBV). The authentic amino acids Pro-79 and Ala-80 of the core protein are removed. Generation of the GFP fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. GFP can be considered as an insertion sequence and the HBV core protein can be considered as an acceptor sequence, which has a deletion. Thus, claims 1-8 are anticipated by Kratz.

7. Claims 1-8 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Lacatena et al., 1994 (PNAS, Vol. 91, pp. 10521-10525).

Claims 1-6 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence. Claims 2-3 specify the state of the insertion sequence is modulated and in response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the insertion sequence, respectively. Claim 6 specifies the fusion molecule comprises a new state. Claims 7-8 are directed to a method for assembling a fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and

selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence. Claim 14 is directed to a method for assembling a multistable fusion molecule which can switch between at least an active state and a less active state comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, wherein the respective other sequence is responsive to a signal, and selecting a fusion molecule, wherein the state is coupled to the signal such that the fusion molecule switches state in response to the signal.

Lacatena teaches using TnphoA, a transposon probe for protein export signals, to generate hubeta2AR-phoA fusion protein in vivo by transposition of TnphoA into the hubeta2AR gene in PUC18. Lacatena examined 23 independent Pho+ hubeta2AR:TnphoA insertions and found 13 different fusion sites in the hubeta2AR molecule. The 13 fusion sites are clustered in the first three transmembrane domains and in the C terminus of the hubeta2AR molecule (e.g. bridging p. 10522-10523). Generation of the hubeta2AR-phoA fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. PhoA can be considered as an insertion sequence and the hubeta2AR (human beta2-adrenergic receptor) protein can be considered as an acceptor sequence, which has a deletion. Lacatena also teaches fusing the coding region of the hubeta2AR gene to the IPTG-inducible lac promoter (e.g. p. 10522, right column). The IPTG-inducible lac promoter is responsive to IPTG. When IPTG is present, the fusion molecule (lac promoter-hubeta2AR gene) switches state in response to the signal (IPTG). Thus, claims 1-8 and 14 are anticipated by Lacatena.

8. Claims 1-8 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al., 2003 (US Patent No. 6,596,485 B2).

The subject matter of claims 1-8 and 14 are as discussed above.

Anderson teaches generating various fusion proteins by fusing GFP or its derivatives or variants into random peptides in such a manner that the structure of the GFP is not significantly perturbed and the peptide is metabolically conformationally stabilized (e.g. column 2, lines 60-67, column 5, lines 3-4). The derivative GFP contains at least one amino acid substitution, deletion or insertion that can occur at any residue within the GFP protein (e.g. column 3, lines 28-34). Anderson also teaches the fusion nucleic acids encoding the fusion polypeptide, and expression vector comprising a transcriptional regulatory sequence operably linked to the nucleic acid encoding the fusion protein, wherein the transcriptional regulatory sequence can be a promoter, such as an inducible promoter, for example Tet regulatory element (e.g. column 18, lines 32-55, column 19, lines 19-27). Generation of the GFP fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. The peptide can be considered as an insertion sequence and the GFP can be considered as an acceptor sequence, which can have a deletion, a substitution or insertion. The inducible promoter, such as Tet regulatory element, is responsive to inducer, such as tetracycline. When inducer, such as tetracycline, is present, the fusion molecule (fusion nucleic acid operably linked to the inducible promoter) switches state in response to the signal (the inducer, such as tetracycline). Thus, claims 1-8 and 14 are anticipated by Anderson.

9. Claims 1-8 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Doi et al., 1999 (FEBS Letters, Vol. 453, p. 305-307).

The subject matter of claims 1-8 and 14 are as discussed above.

Doi teaches generation of GFP-based sensors by inserting a desired molecular-recognition domain into a loop of GFP. In the absence of the target molecule, conformational fluctuations of the inserted domain put stress on the GFP scaffold with a consequent reduction in fluorescence, however, the binding of a target molecule stabilizes the conformation of the inserted domain, resulting in restoration of the GFP fluorescence (e.g. Figure 1). Doi teaches preparation of expression vector expressing GFP-TEM1 beta-lactamase (GFP-Bla) fusion protein with Bla inserted between Gln-172 and Asp-173 of GFP. Doi also teaches preparation of expression vector comprising a Bla inhibitory protein (BLIP) coding sequence under the control of an inducible promoter, P_{BAD} promoter from E. coli JM109, that is inducible with L-arabinose and is repressed by D-glucose (e.g. p. 305, right column, 2nd and 3rd paragraphs). Random mutagenesis of the fusion GFP:Bla gene was performed using error-prone PCR and the PCR product was inserted in place of the GFP gene on pND101 to obtain a plasmid library. The clone that shows largest difference of fluorescence on the LB-arabinose plate and the LB-glucose plate are selected (e.g. p. 305, right column, 3rd paragraph). Generation of the GFP fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. The Bla can be considered as an insertion sequence and the GFP can be considered as an acceptor sequence, which can have a deletion, a substitution or insertion. The P_{BAD} inducible promoter is responsive to inducer, i.e. L-arabinose. When the

inducer, L-arabinose, is present, the fusion molecule (BLIP gene under the control of the inducible promoter) switches state in response to the signal (the inducer, L-arabinose). Thus, claims 1-8 and 14 are anticipated by Doi. Furthermore, the BLIP protein can be considered as a signal. When expressed BLIP protein binds to Bla protein within the GFP-Bla fusion protein, it restores the fluorescence of GFP, thus, the fusion molecule (GFP-Bla fusion protein) switches state in response to the signal (BLIP protein). Therefore, claims 1-8 and 14 are anticipated by Doi.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER